REMARKS

The invention relates to the identification and characterization of two classes of bone marrow stem cells: 1) small and rapidly self-renewing stem cells (RS cells), and 2) large, more mature marrow stromal cells (mMSC cells). The invention also relates to methods of their use.

Claims 1 through 10 are pending in the present application. Claims 4-8 and 10 have been withdrawn from consideration as being drawn to a non-elected invention. Therefore, claims 1-3 and 9 are currently under examination.

Claims 1 and 9 have been amended herein to recite a population of cells enriched for human small and rapidly self-renewing stem cells (RS), wherein about 95% of the cells in said population are RS cells. Support for the amendments to claims 1 and 9 is found throughout the as-filed specification as fully set forth below. As such, no new matter has been added by way of the present Amendment.

Rejection of claims 1-3 and 9 pursuant to 35 U.S.C. §112, first paragraph – enablement

Claims 1-3 and 9 stand rejected pursuant to 35 U.S.C. §112, first paragraph, as lacking enablement. As an initial matter, the Examiner assets that the specification discloses human RS cells and therefore contends that the claims should recite "human" cells. The Examiner also asserts that the specification does not adequately provide guidance as to how one skilled in the art would isolate a "homogenous" population of RS cells. While not necessarily agreeing with the Examiner's reasoning, but rather in a good faith effort to expedite the prosecution of the present application, Applicants have amended claims 1 and 9 to recite a population of cells enriched for human small and rapidly self-renewing stem cells (RS), wherein about 95% of the cells in said population are RS cells. Applicants respectfully submit that claims 1-3 and 9 as amended are enabled under 35 U.S.C. §112, first paragraph, for the following reasons.

The invention relates to the discovery that bone marrow contains at least two kinds of stem cells, hematopoietic stem cells and stem cells for nonhematopoietic tissues, referred to as mesenchymal stem cells (MSCs). The present application discloses that human mesenchymal stem cells (hMSCs) are comprised of two additional classes of cells: 1) small and rapidly self-renewing stem cells (RS cells) and 2) large, more mature cells (mMSCs). Therefore,

in the context of RS cells, and as encompassed in the amended claims, a population of cells enriched for human small and rapidly self-renewing stem cells (RS), wherein about 95% of the cells in said population are RS cells, is a cell population that is substantially free of others cells derived from bone marrow, for example hematopoietic stem cells and mMSCs. The Examiner contends that the population of RS cells per se, is comprised of a population of RS-1 and RS-2 cells, and therefore constitutes a heterogeneous population. Applicants point out that the alleged heterogeneous population of RS cells (including both RS-1 and RS-2 cells) are substantially homologous with respect to the mixture of cells derived from bone marrow as isolated by their unique protein expression profile. For example, the specification teaches that RS cells contain surface epitopes not found on mMSC, which is the second class of cell present in a mixed population of MSCs. Further, the specification teaches surface markers present on mMSCs which are not present on RS cells. Therefore, the specification would teach one skilled in the art how to isolate a population of RS cells as encompassed in the amended claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Under the present patent law, claims 1-3 and 9 as amended are enabled under 35 U.S.C. §112, first paragraph. Support for the amendments to claims 1 and 9 is found throughout the specification as filed. Particularly, the specification, beginning at page 2, line 16; and page 6, lines 1 through 23, discloses that the RS cells are prepared by lifting 14 day cultures of marrow stromal cells (MSCs) and passing these cells through a 10 micron filter. A FACS analysis demonstrated that about 95% of the cells were RS cells. Therefore, these amendments are supported by the disclosure provided in the specification as filed, and no new matter has been added by way of these amendments.

Furthermore, the disclosure provided by the specification as filed amply supports claims encompassing a population of cells enriched for RS cells. The skilled artisan, when armed with the methods disclosed in the specification, the identification of unique RS cell polypeptides and surface epitopes with respect to other cells derived from bone marrow, and the methods of identifying such polypeptides and surface epitopes as provided by the disclosure in the specification as filed, would have been able to isolate, enrich, and characterize, through routine experimentation, a population of cells enriched for human RS cells, wherein about 95% of the cells in said population are RS cells. The skilled artisan would also have been able to practice the invention commensurate with the scope of the claims without undue experimentation.

One of skilled in the art would also have been able to produce a population of cells enriched for RS cells using the series of unique RS surface epitopes and polypeptides to distinguish and isolate RS cells from a population of MSCs, including a population of large, more mature marrow stromal cells (mMSC). Based on the disclosure of the as-filed specification, one skilled in the art would have been able to use such teachings set forth in the specification as filed and/or as known in the art, such as FACS assays, to identify and enrich for a population of cells encompassing about 95% RS cells from a mixed population of MSCs derived from bone marrow. The teachings of the present invention, for example, the discovery that RS cells can be distinguished from mMSCs by their protein expression profiles and by their unique surface markers (epitopes) to isolate a progenitor cell population, are amply disclosed in the specification as filed (*see*, *e.g.*, page 2, line 18; page 4, lines 3-15; page 7, lines 13 through page 8, line 11). The as-filed specification provides the prescribed unique RS polypeptides and surface markers useful for arriving at the cell population of the present invention. As such, when armed with the list of polypeptides and surface markers, a skilled artisan would be able to arrive at the cells of the present invention using methods disclosed in the as-filed specification and methods known to those skilled in the art, and the practice of such methods is routine in the art and should not be considered an undue burden.

In sum, claims 1-3 and 9, are enabled by the disclosure provided in the specification as filed as required under 35 U.S.C. §112, first paragraph. Therefore, Applicants respectfully request that the rejection of these claims be reconsidered and withdrawn.

Rejection of claims 1-3 and 9 pursuant to 35 U.S.C. §112, first paragraph – written description

The Examiner has rejected claims 1-3 and 9, under 35 U.S.C. §112, first paragraph, as lacking written description. Specifically, the Examiner contends that although the specification contemplates a homogenous population of cells, it does not describe a homogenous population of RS cells because the specification recites a heterogeneous population of RS cells. As discussed above, Applicants contend that the alleged heterogeneous population of RS cells is in fact homogenous in the context of RS cells with respect to the mixed population of cells derived from bone marrow. In any event, claims 1 and 9 have been amended as discussed herein.

Applicants respectfully submit that the extensive disclosure in the specification as filed, provides ample written description for claims reciting a population of RS cells, wherein about 95% of the cells in the population are RS cells (see the specification on page 2, line 16, and page 6, lines 1-23). Therefore, there is ample written description in the specification as filed for claims relating to such a cell population, and these claims therefore satisfy the written description requirement of 35 U.S.C. §112, first paragraph. Applicants respectfully request that the rejection of these claims be reconsidered and withdrawn.

Rejection of claim 9 pursuant to 35 U.S.C. § 112, second paragraph

Claim 9 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner indicates that claim 9 lacks antecedent basis for the recitation of "said population of MSC" and "said MSC cell population." Applicants have amended claim 9 to recite "mMSC" to properly and distinctly claim the subject matter of the present invention. Applicants respectfully submit that the rejection of claim 9 based on lack of antecedent basis is rendered moot in view of the amendment to claim 9 and should be withdrawn.

Rejection of claims 1-3 and 9 pursuant to 35 U.S.C. §102(b)

The Examiner has rejected claims 1-3 and 9 under 35 U.S.C. § 102(b) as being anticipated by Bruder et al. (1997, J. of Cell. Biochem. 64:278-294). Specifically, the Examiner contends that Bruder et al. teaches a population of human mesenchymal stem cells (hMSCs) that would inherently have the property for the expression of FLK-1, TRK, transferrin receptor, and

annexin II. The Examiner is of the opinion that the pending claims comprise hMSCs, and therefore the Examiner reasons that the cells of Bruder anticipate the claimed cell population. Applicants point out that instead, the present invention relates to a population of cells enriched for human RS cells, whereby the cell population is a more homogenous population of hMSCs. Based on the disclosure of the as-filed specification, hMSCs are heterogenous in nature in that they contain at least two different type of cells, while the present invention relates to a more homogenous population of a subset cell population present in the mixed population of hMSCs. In any event, Applicants respectfully submit that Bruder does not anticipate the present invention for the following reasons.

It is hornbook law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). Therefore, Bruder must describe each and every element of claims 1-3 and 9, in order to anticipate these claims under 35 U.S.C. §102(b), and this reference does not.

Applicants contend that the Examiner has misinterpreted the reference of Bruder et al. to anticipate the present invention under 35 U.S.C. §102(b). The Examiner asserts that Bruder discloses a homogenous population of hMSCs. However, Applicants respectfully point out that the claims as amend recite a population of RS cells, which is a more homogenous subset cell population of hMSCs. Prior to the disclosure of the present invention, one skilled in the art would not have been able to obtain a population of cells wherein the population of cells contains about 95% RS cells because there would not have been any means to isolate RS cells from a population of hMSCs without the teachings set forth in the as-filed specification.

Applicants also submit that the alleged homogenous population of hMSCs described in Bruder et al. is actually a mixed population of cells which cannot contain about 95% RS cells. Even if Bruder discloses a cell having characteristics of an RS cell, which Bruder does not, Bruder does not teach a subpopulation of RS cells, yet alone an enriched population of cells having about 95% RS cells. At best Bruder describes a population of hMSCs and methods for

culturing hMSCs. Therefore, Bruder does not disclose each and every element of the claimed invention.

The Examiner has also rejected claims 1-3 and 9 pursuant to 35 U.S.C. §102(b) as being anticipated by Pittenger et al. (1999 Science 284:143-147). Specifically, the Examiner asserts that Pittenger discloses an isolated population of homogenous human mesenchymal stem cells. Similar to Bruder et al., Pittenger does not teach a subset population of mesenchymal stem cells, yet alone an enriched population of RS cells. As discussed above, MSCs contain at least two other cell types, where RS cells are a subset population of cells within the population of MSCs. The present invention encompasses a population of RS cells that is substantially free of mMSCs. Pittenger does not disclose a population of MSCs that are free of mMSCs, but rather discloses a population of MSCs that are free of adult hematopoietic stem cells (HSCs). The skilled artisan would understand that the MSC cell population disclosed by Pittenger includes a substantial amount of mMSCs. Nowhere does Pittenger even teach a subset population of cells within a population of MSCs.

Therefore, neither Bruder nor Pittenger anticipate the present invention because these references do not disclose each and every element of the claimed invention. Reconsideration and withdrawal of the Examiner's rejection of claims 1-3 and 9 pursuant to 35 U.S.C. §102(b) is respectfully requested at this time.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 1-3 and 9 are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

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Enclosures: Petition for extension of time
RCE